Cochrane Database of Systematic Reviews

Intraventricular antibiotics for bacterial meningitis in neonates (Review)

Shah SS, Ohlsson A, Shah VS

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Intraventricular antibiotics for bacterial meningitis in neonates

Sachin S Shah[1], Arne Ohlsson[2a], Vibhuti S Shah[3]

[1]Department of Pediatrics, Surya Hospital for Women and Children, Pune, India. [2]Departments of Paediatrics, Obstetrics and Gynaecology and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada. [3]Department of Paediatrics and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

[a]Deceased

Contact address: Sachin S Shah, Department of Pediatrics, Surya Hospital for Women and Children, Pune, India. sshahdoc@gmail.com.

A B S T R A C T

Background

Neonatal meningitis may be caused by bacteria, especially gram-negative bacteria, which are difficult to eradicate from the cerebrospinal fluid (CSF) using safe doses of antibiotics. In theory, intraventricular administration of antibiotics would produce higher antibiotic concentrations in the CSF than intravenous administration alone, and eliminate the bacteria more quickly. However, ventricular taps may cause harm.

Objectives

To assess the effectiveness and safety of intraventricular antibiotics (with or without intravenous antibiotics) in neonates with meningitis (with or without ventriculitis) as compared to treatment with intravenous antibiotics alone.

Search methods

The Cochrane Library, Issue 2, 2007; MEDLINE; EMBASE; CINAHL and Science Citation Index were searched in June 2007. The Oxford Database of Perinatal Trials was searched in June 2004. Pediatric Research (abstracts of proceedings) were searched (1990 to April 2007) as were reference lists of identified trials and personal files. No language restrictions were applied.

This search was updated in May 2011.

Selection criteria

Selection criteria for study inclusion were: randomised or quasi-randomised controlled trials in which intraventricular antibiotics with or without intravenous antibiotics were compared with intravenous antibiotics alone in neonates (< 28 days old) with meningitis. One of the following outcomes was required to be reported: mortality during initial hospitalisation; neonatal or infant mortality, or both; neurodevelopmental outcome; duration of hospitalisation; duration of culture positivity of CSF and side effects.

Data collection and analysis

All review authors abstracted information for outcomes reported and one review author checked for discrepancies and entered data into RevMan 5.1. Risk ratio (RR), risk difference (RD), number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH), and mean difference (MD), using the fixed-effect model are reported with 95% confidence intervals (CI).

Main results

The updated search in June 2011 did not identify any new trials. One study is included in the review. This study assessed the effect of intraventricular gentamicin in a mixed population of neonates (69%) and older infants (31%) with gram-negative meningitis and ventriculitis. Mortality was statistically significantly higher in the group that received intraventricular gentamicin in addition to intravenous antibiotics compared to the group receiving intravenous antibiotics alone (RR 3.43; 95% CI 1.09 to 10.74; RD 0.30; 95% CI 0.08 to 0.53); NNTH 3; 95% CI 2 to 13). Duration of CSF culture positivity did not differ significantly (MD -1.20 days; 95% CI -2.67 to 0.27).

Authors' conclusions

In one trial that enrolled infants with gram-negative meningitis and ventriculitis, the use of intraventricular antibiotics in addition to intravenous antibiotics resulted in a three-fold increased RR for mortality compared to standard treatment with intravenous antibiotics alone. Based on this result, intraventricular antibiotics as tested in this trial should be avoided. Further trials comparing these interventions are not justified in this population.

PLAIN LANGUAGE SUMMARY

Intraventricular antibiotics for bacterial meningitis in neonates

Infection of the membranes and the fluid surrounding the brain (meningitis) and of the fluid-filled spaces in the brain (ventriculitis) may be caused by bacteria, especially gram-negative bacteria. This type of infection is difficult to eradicate using safe doses of antibiotics given into the blood stream. In theory, intraventricular administration of antibiotics (administration of antibiotics into the fluid-filled spaces in the centre of the brain) would produce higher antibiotic concentrations in the fluid in the brain than intravenous administration alone, and eliminate the bacteria more quickly. However, taps of the fluid-filled spaces may cause harm as the needle has to penetrate the brain tissue. Only one trial was identified. In this trial enrolling infants with gram-negative meningitis and ventriculitis, the use of intraventricular antibiotics in addition to intravenous antibiotics resulted in a three-fold increased risk for mortality compared to standard treatment with intravenous antibiotics alone. Based on this result, intraventricular antibiotics should be avoided. Further trials comparing these interventions are not justified in newborn infants.

BACKGROUND

Description of the condition

Bacterial meningitis is more common in the first month of life than at any other age (Pong 1999). The epidemiology of meningitis in the neonatal period is similar to that of neonatal sepsis. Meningitis can occur as a part of sepsis in both the early and late-onset time periods or as focal infection as late-onset disease (Pong 1999; Klein 2000). The incidence of neonatal bacterial meningitis ranges from 0.25 per 1000 live births to 1 per 1000 live births (Bell 1989; Hristeva 1993). Meningitis occurs in approximately 25% of neonates with bacteraemia (Klein 2000). The risk factors for meningitis include preterm birth, maternal chorioamnionitis, prolonged pre-labour rupture of foetal membranes and presence of a foreign body such as a cerebrospinal fluid (CSF) shunt (Ronan 1995; Klein 2000).

Group B β-haemolytic streptococci (GBS), gram-negative enteric bacteria and *Listeria monocytogenes* are the most common agents causing meningitis (Pong 1999). Infection with gram-negative bacilli accounts for 30% to 40% of cases of meningitis (Dawson 1999), with *Escherichia coli* (*E. coli*) being the most common organism isolated (50% of all gram-negative isolates) (Anderson 1990; Unhanand 1993; Dawson 1999) followed by *Klebsiella* species (Klein 2000). Other organisms that have been implicated to cause meningitis include enterobacter, citrobacter and serratia species (Polin 2001). Meningitis with organisms such as coagulase-negative staphylococcus and pseudomonas species (Polin 2001) is more common in neonates requiring prolonged hospitalisation, need for central venous catheters, parenteral nutrition and ventilatory support.

Description of the intervention

Prior to the availability of antibiotics, bacterial meningitis was a uniformly fatal disease (Flexner 1913; Scheld 1984). The development of modern methods of intensive care and newer antibiotics resulted in decline in mortality to 10% to 25% in infancy (Dawson 1999; Harvey 1999; Heath 2003). However, the incidence of neurological morbidity in infants who survive bacterial meningitis is high, ranging from 20% to 80%, and is somewhat dependent on the infecting organism (Harvey 1999; Klinger 2000; Heath 2003). Acute complications of meningitis include death, seizures, ventriculitis, hydrocephalus, subdural effusion and brain abscess (Baumgartner 1983; Hristeva 1993). The disease is often more severe with gram-negative bacteria than gram-positive bacteria, with higher rates of both mortality and morbidity (Franco 1992). Gram-negative meningitis results in prolonged duration of CSF bacterial culture positivity compared to GBS. A delay in achieving CSF sterilisation has been shown to be associated with increased neurological sequelae (McCracken 1972; Unhanand 1993). Long-term sequelae among survivors of meningitis include hydrocephalus, developmental delay, cerebral palsy, seizures requiring anticonvulsant therapy, decreased visual acuity and hearing loss (Baumgartner 1983; Hristeva 1993).

For these reasons, antibiotic therapy for meningitis should be aggressive. The doses used must achieve a bactericidal concentration of antibiotic in the CSF. The standard therapy for neonatal meningitis is intravenous administration of antibiotics. Efficient elimination of bacteria depends not only on the ability of an antibiotic to enter the CSF, but also on the relationship between the concentration of antibiotic in the CSF and the minimal bactericidal concentration (MBC) for the infecting pathogen. Therefore, while gentamicin can enter CSF relatively readily (CSF/serum concentration 20% to 25%), the concentrations achieved in CSF are close to the MBC only for susceptible organisms (McCracken 1982; Polin 2001). In contrast, β-lactam antibiotics such as penicillins or cephalosporins enter CSF less readily, but because larger doses can be used without toxicity, the concentrations achieved are far higher than the MBC (Polin 2001). Since CSF drug concentrations can lag behind serum drug levels, a single measurement may underestimate the true ability of a drug to enter the CSF. The more reliable estimate is the area under concentration curve, but that requires multiple CSF samples and cannot be routinely done in humans (Polin 2001).

The initial choice of intravenous antibiotics for neonates with suspected meningitis must cover both gram-positive and gram-negative organisms (Quagliarello 1997). Therefore, empiric therapy generally includes ampicillin in addition to either an aminoglycoside or a third-generation cephalosporin. Once a pathogen has been isolated, antibiotic therapy for bacterial meningitis can be tailored to the pathogen.

How the intervention might work

In theory, the intraventricular route of administration of antibiotics would achieve higher antibiotic concentrations in the CSF and eliminate the bacteria more quickly. In a prospective study of 16 infants with neonatal meningitis, Lee and co-workers (Lee 1977) used a combination of systemic and intraventricular antibiotics. Fifteen infants survived the infection and, of these infants, seven were normal on follow-up. There were no acute adverse reactions after the use of intraventricular antibiotics. A retrospective review of gram-negative meningitis in neonates demonstrated that the mortality was lower after intraventricular plus systemic antibiotic therapy than after systemic antibiotic therapy alone (Wright 1981). The authors suggested that if careful attention is given to the pharmacokinetics of intraventricular therapy, this route may be a valuable adjunct to therapy for gram-negative meningitis. Techniques used for intraventricular drug administration in these trials included repeated ventricular taps, open or closed implanted catheter, or use of Omaya or Rickham reservoir. Intraventricular antibiotics have also been used in children with CSF shunt infection with variable results (James 1980; Stamos 1993) and controversy exists as to the best treatment of shunt infections. Several therapeutic modalities are currently used for the treatment of shunt infections including: 1) intravenous antibiotics with/without intrashunt antibiotics with shunt removal and external ventricular drain or ventricular taps, 2) intravenous antibiotics with/without intrashunt antibiotics with shunt removal and immediate replacement and 3) intravenous antibiotics with/without intrashunt antibiotics without removal of the infected shunt (James 1980; Whitehead 2001).

Although we could not identify any new trials in 2011 for this update of our review, we did identify one retrospective study of interest to this review. Arnell 2007 reported on a retrospective study of the management of shunt infection in children. The authors followed a protocol that included a two-stage procedure involving externalisation of the ventricular catheter in combination with intraventricular and systemic administration of antibiotic medication followed by shunt replacement. Intraventricular treatment consisted of daily instillations of vancomycin or

gentamicin with trough concentrations held at high levels of 7 to 17 mg/L for both antibiotic agents.

During a 13-year study period, the authors treated 34 consecutive intraventricular shunt infections in 30 children. Ten of the children were initially treated with intravenous antibiotic therapy for at least three days, but this treatment did not sterilise the CSF. After externalisation of the ventricular catheter, high-dose intraventricular treatment was given for a median of eight days (range three to 17 days) before shunt replacement.

The CSF was found to be sterile in one of three, seven of eight, 20 of 20, and six of six cases after one, two, three and more than three days' treatment, respectively. In no case was any subsequent culture positive after a negative result had been obtained. Clinical symptoms resolved in parallel with the sterilisation of the CSF. There were no relapses or deaths during the six-month follow-up period, and there have been none as of April 2007.

The study authors concluded that despite the ventricular catheter being left in place and the short duration of therapy, the treatment regimen described by the authors resulted in quick sterilisation of the CSF, a low relapse rate, and survival of all patients in this series.

However, a ventricular tap for the administration of antibiotics is an invasive procedure that is associated with its own risks. Repeated needle aspirations of ventricular fluid have been associated with development of porencephalic cysts (Salmon 1967). In healthy adult rabbits, Watanabe and co-workers were consistently able to produce widespread axonal degeneration, myelin swelling and glia-cell necrosis after intracisternal inoculation of gentamicin (Watanabe 1978).

Why it is important to do this review

Studies have been conducted in neonates with bacterial meningitis with the hypothesis that larger concentrations of drug resulting from direct inoculation into the CSF space would sterilise cultures more rapidly and improve outcome from the disease. This systematic review evaluates the evidence from those trials.

O B J E C T I V E S

Primary objective

To determine the effectiveness and safety of intraventricular antibiotics (with or without intravenous antibiotics) in neonates with meningitis (with or without ventriculitis) as compared to conventional treatment with intravenous antibiotics alone.

To assess the effectiveness and safety of intraventricular antibiotics, the following separate comparisons were planned:

- intraventricular antibiotics alone vs. intravenous antibiotics alone,
- intraventricular plus intravenous antibiotics vs. intravenous antibiotics alone,
- infants with or without a CSF shunt (e.g. ventricular peritoneal shunt, ventriculostomy reservoir, etc.).

Secondary objectives

To determine in subgroup analyses the effectiveness and safety of intraventricular antibiotics in relation to the following criteria:

- gestational age (< 37 weeks and ≥ 37 weeks) or birth weight (< 2500 g and ≥ 2500 g),
- presence or absence of documented ventriculitis,
- type of infecting organism (gram-positive or gram-negative organisms),
- type of antibiotic used (aminoglycosides, cephalosporins, etc.).

M E T H O D S

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Term or preterm (< 37 weeks' gestational age) infants in the neonatal period (< 28 days) with bacterial meningitis with or without ventriculitis.

The criteria for diagnosis of bacterial meningitis should include the following:

1. positive CSF culture or positive gram stain, or both.

The criteria for diagnosis of ventriculitis should include one of the following:

1. positive ventricular fluid culture;
2. leukocytosis (> 50 cells/mm^3) with/without organisms identified on gram staining.

Types of interventions

The intervention should be intraventricular administration of any antibiotic (of any duration) with or without intravenous antibiotic treatment compared with intravenous antibiotic treatment alone. The antibiotic used for intraventricular administration may/may not be the one used for intravenous therapy.

Types of outcome measures

Primary outcomes

1. All-cause mortality during the hospital stay.

Secondary outcomes

1. Neonatal mortality (death during the first 28 days of life).
2. Infant mortality (death during the first year of life).
3. Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardised and validated assessment tool or a child developmental specialist, or both) at any age (outcome data will be grouped at 12, 18 and 24 months if available).
4. Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death).
5. Duration of culture positivity of CSF.
6. Antimicrobial side effects (diarrhoea, fungal infection, anaphylaxis etc.).
7. Any side effects not listed as an outcome above but reported by the study authors as a side effect.

Search methods for identification of studies

See: Cochrane Neonatal Review Group search strategy.

MEDLINE database (1966 to June 2007) was searched using MeSH terms: "infant, newborn" AND "meningitis" AND "intraventricular" AND "antibiotics" AND (random allocation OR controlled trial OR randomised controlled trial). The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2007), EMBASE (1980 to June 2007) and CINAHL (1982 to June 2007), and abstracts (American Pediatric Society and European Society for Paediatric Research annual meetings) published in *Pediatric Research* (1990 to April 2007) were searched either manually or electronically in the PAS Abstract Archive (2000 to 2007). The reference lists of identified trials were searched to identify potential articles for inclusion. Science Citation Index was searched on the reference to the only trial found (McCracken 1980). The Oxford Database of Perinatal Trials was searched for the initial review. Unpublished data were not sought, but authors of published trials were to be contacted to clarify or provide additional information. No language restrictions were applied. The retrieved articles were screened by the three review authors to identify articles eligible for inclusion in this review.

In May 2011, we updated the search. See Appendix 1.

Data collection and analysis

We used the standard review methods of the Cochrane Neonatal Review Group.
All abstracts and published studies identified as potentially relevant by the literature search were assessed for inclusion in the review by the two review authors (SS, AO).

Selection of studies

We assessed all abstracts and published full reports identified as potentially relevant by the literature for inclusion in the review.

Data extraction and management

If studies were identified, each review author would extract data separately on a data abstraction form. The information would then be compared and differences would be resolved by consensus. One review author (AO) would enter data into RevMan 5.1 (RevMan 2011) and the other author (SS) would cross check the printout against his own data abstraction forms and errors would be corrected.

For the studies identified as abstracts, primary authors were to be contacted to ascertain whether a full publication was available if the full paper was not identified in an electronic data base. The primary author of the identified trial (McCracken 1980) was contacted for additional information.

Assessment of risk of bias in included studies

Quality assessments of the retrieved articles were conducted by the review authors, who were not blinded to authors, institution or journal of publication. The quality of included trials was evaluated independently by the review authors, using the following criteria:

Selection bias (random sequence generation and allocation concealment).

Adequate sequence generation?

For each included study, we would categorise the risk of selection bias as:

- low risk - adequate (any truly random process, e.g. random number table; computer random number generator);
- high risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk - no or unclear information provided.

Allocation concealment?

For each included study, we would categorise the risk of bias regarding allocation concealment as:

- low risk - adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk - no or unclear information provided.

Blinding?

Performance bias: for each included study, we would categorise the methods used to blind study personnel from knowledge of which intervention a participant received (as our study population consisted of neonates they would all be blinded to the study intervention.):

- low risk - adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group);
- high risk - inadequate - personnel aware of group assignment;
- unclear risk - no or unclear information provided.

Detection bias: for each included study, we would categorise the methods used to blind outcome assessors from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention). Blinding would be assessed separately for different outcomes or classes of outcomes. We would categorise the methods used with regards to detection bias as:

- low risk - adequate; follow-up was performed with assessors blinded to group;
- high risk - inadequate; assessors at follow-up were aware of group assignment;
- unclear risk - no or unclear information provided.

Incomplete data addressed?

Attrition bias: for each included study and for each outcome, we would describe the completeness of data including attrition and exclusions from the analysis. We would note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we would re-include missing data in the analyses. We would categorise the methods with respect to the risk of attrition bias as:

- low risk - adequate (< 10% missing data);
- high risk - inadequate (> 10% missing data);
- unclear risk - no or unclear information provided.

Free of selective reporting?

Reporting bias

For each included study, we would describe how we investigated the risk of selective outcome reporting bias and what we found. We would assess the methods as:

- low risk - adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk - inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk - no or unclear information provided (the study protocol was not available).

Free of other bias?

Other bias: for each included study, we would describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We would assess whether each study was free of other problems that could put it at risk of bias as:

- low risk - no concerns of other bias raised;
- high risk - concerns raised about multiple looks at the data with the results made known to the investigators, difference in number of patients enrolled in abstract and final publications of the paper;
- unclear - concerns raised about potential sources of bias that could not be verified by contacting the authors.

Overall risk of bias?

We would make explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would assess the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We would explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

The statistical analyses followed the recommendations of the Cochrane Neonatal Review Group and were performed using the RevMan 5.1 software. The estimates of treatment effects included risk ratio (RR), risk difference (RD), number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for dichotomous outcomes, and weighted mean difference (WMD) (or mean difference (MD) if only one trial was included) for continuous outcomes. All estimates of treatment effects are reported with 95% confidence intervals (CI). A fixed-effect model was to be used for meta-analyses.

Unit of analysis issues

The unit of analysis would be the individual patient.

Dealing with missing data

If we had identified trials with missing data, we would approach the authors to provide us with additional information.

Assessment of heterogeneity

Heterogeneity tests would be performed to assess the appropriateness of pooling the data. Results of the I^2 statistic would be reported.

Assessment of reporting biases

If at least 10 trials were included in one meta-analysis we would perform a funnel plot. If there was asymmetry, we would try and explain it based on study characteristics.

Data synthesis

We planned to perform statistical analyses according to the recommendations of the Cochrane Neonatal Review Group (neonatal.cochrane.org/en/index.html). We planned to analyse all infants randomised on an intention-to-treat basis. We planned to analyse treatment effects in the individual trials. We planned to use a fixed-effect model for meta-analysis in the first instance to combine the data. Where substantial heterogeneity existed, the potential cause of heterogeneity would be examined in subgroup and sensitivity analyses. When we judged meta-analysis to be inappropriate, we planned to analyse and interpret individual trials separately. For estimates of typical RR and RD, we would use the Mantel-Haenszel method. For measured quantities, we would use the inverse variance method.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were to be performed according to the criteria listed under objectives.

To assess the effectiveness and safety of intraventricular antibiotics, the following separate comparisons were planned:

- intraventricular antibiotics alone versus intravenous antibiotics alone;
- intraventricular plus intravenous antibiotics versus intravenous antibiotics alone;
- infants with or without a CSF shunt (e.g. ventricular peritoneal shunt, ventriculostomy reservoir, etc.).

Secondary objectives:
To determine in subgroup analyses the effectiveness and safety of intraventricular antibiotics in relation to the following criteria:

- gestational age (< 37 weeks and ≥ 37 weeks) or birth weight (< 2500 g and ≥ 2500 g);
- presence or absence of documented ventriculitis;
- type of infecting organism (gram-positive or gram-negative organisms);
- type of antibiotic used (aminoglycosides, cephalosporins, etc.).

Sensitivity analysis

No sensitivity analyses were planned a priori, but could be conducted depending on the results.

RESULTS

Description of studies

The literature search did not identify any study that strictly met all of the inclusion criteria either in June 2004 or in the updated searches in June 2007 and May 2011. However, one randomised controlled trial conducted in both neonates and infants was identified (McCracken 1980). Outcomes specific to the different age groups could not be abstracted. The primary author was contacted and asked whether data for the infants < 28 days could be provided. He responded that he no longer had the original data from that study. We chose to deviate from our protocol and included this study in this systematic review as 69% of the randomised infants with ventriculitis were less than 30 days old at the time of enrolment. The study was conducted in 20 institutions in the US and Latin America more than 25 years ago. The rationale for enrolling only infants with meningitis caused by gram-negative bacteria was based on the high mortality in this population and the longer duration of CSF positivity in meningitis caused by gram-negative bacteria compared to gram-positive bacteria. Higher concentrations of gentamicin for longer duration in intraventricular fluid following intraventricular injection had previously been found in adults, justifying this trial in infants. Eighty-seven infants were considered for enrolment in the study but 16 were found unacceptable (see Characteristics of included studies table for details). The remaining 71 infants had ventricular taps and lumbar punctures. Nineteen did not have ventriculitis and these infants were assigned to receive systemic antibiotics plus lumbar intrathecal gentamicin or systemic antibiotics only. The latter stratum was not included in this review as neither group received intraventricular antibiotics. Fifty-two infants with meningitis (caused by gram-negative enteric bacilli) and ventriculitis (diagnosed by ≥ 50 white cells/mL ventricular fluid with or without gram-negative rods on stained smear or culture of ventricular fluid) were randomly allocated to receive either intraventricular antibiotics plus intravenous antibiotics or intravenous antibiotics alone. Only these 52 infants are included in this review. The most commonly isolated bacteria were *E coli* (38.5%), Klebsiella-enterobacter and citrobacter (28.8%), and Salmonella (19.2%). Other organisms were found in 13.5% of the infants. Outcomes that were reported included mortality during hospital stay, days of positive CSF cultures (obtained from intraventricular or lumbar CSF samples, or both) and morbidity on follow-up examinations.

Risk of bias in included studies

In the included study (McCracken 1980) the allocation of the study subjects to the two interventions was concealed. The researchers/health care providers could not be blinded to the interventions. It is unclear whether the outcome assessments, specifically the long-term assessments, were performed blinded to group assignment. Survivors were scheduled for follow-up evaluations six and 12 months after illness and yearly thereafter. Complete physical, neurological, and Denver developmental examinations were to be done at each visit. The Cattell infant intelligence and Gessell fine and gross motor developmental tests were administered to some infants aged 12 months or more. The study authors do not state the age of the infants/children at the time of their follow-up and the number of children who underwent which exam/test. No sample-size calculation or any pre-determined stopping rules were

reported. The study was terminated early because of the higher mortality rate in the intraventricular-therapy group.

Effects of interventions

Intraventricular plus intravenous antibiotics versus intraventricular antibiotics alone (Comparison 1)

One study (McCracken 1980) was included for this comparison.

Primary outcome

All-cause mortality during hospital stay (Outcome 1.1)

The mortality was statistically significantly higher in the group that received intraventricular antibiotics and intravenous antibiotics compared to the group that received intravenous antibiotics only (Analysis 1.1). The RR was 3.43 (95% CI 1.09 to 10.74); RD was 0.30 (95% CI 0.08 to 0.53) and NNTH was 3 (95% CI 2 to 13). In a secondary publication (McCracken 1980), the same group reported increased endotoxin and interleukin-1β concentrations in CSF of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. This subgroup of 21 patients, of which 10 received intraventricular plus intravenous antibiotics and 11 received intravenous antibiotics alone, were included in the original trial (McCracken 1980). The authors proposed that intraventricular gentamicin may cause release of endotoxin from gram-negative bacilli in ventricular CSF, resulting in increased interleukin-1β concentrations and inflammation, which could have contributed to the poor outcome in these patients.

Secondary outcomes

Neonatal mortality (death during the first 28 days of life)

Data for this outcome could not be abstracted.

Infant mortality (death during the first year of life)

Data for this outcome could not be abstracted. Most deaths occurred within 14 days after the therapy was started. One infant/child died 36 days after the therapy was started from aspiration pneumonia and one from recurrence of meningitis 199 days following enrolment in the study. These deaths could have occurred beyond one year of age.

Neurodevelopmental outcome

Neurodevelopmental outcome (assessed by a standardised and validated assessment tool or a child developmental specialist, or both) at any age (outcome data to be grouped at 12, 18 and 24 months if available.)

It is unclear how old the infants were when assessed for long-term morbidity. We contacted the primary author, but the research team no longer had the original data to make clarifications.

Duration of hospitalisation (total length of hospitalisation from birth to discharge home or death)

This outcome was not reported.

Duration of culture positivity of CSF (Outcome 1.2)

There was no statistically significant difference in the days of positive CSF cultures (ascertained by ventricular or lumbar CSF specimens, or both) (MD -1.20 days; 95% CI -2.67 to 0.27) with a trend favouring the intraventricular plus intravenous antibiotics

group compared to the intravenous antibiotics only group (Analysis 1.2).

Antimicrobial side effects (diarrhoea, fungal infection, anaphylaxis, etc.)

None of these potential side effects were reported, but the authors speculate that the increased case-fatality rate in the intraventricular antibiotics group could be related to the procedure or to a direct toxic effect of gentamicin. See also information under "All-cause mortality during the hospital stay" above.

Intraventricular antibiotics alone versus intravenous antibiotics alone

Infants with or without a CSF shunt

No eligible studies were found that allowed us to undertake either of these planned comparisons.

Planned subgroup analyses

None of the planned subgroup analyses (by gestational age or birth weight classes, presence or absence of ventriculitis, type of organism or antibiotic used) could be conducted, because of lack of eligible data.

DISCUSSION

In this review we could compare intraventricular antibiotics plus intravenous antibiotics with intravenous antibiotics alone only in infants with confirmed ventriculitis/meningitis due to gram-negative organisms. This is likely to be the population that most justifies the intervention that was studied. In theory, the intraventricular route of administration of antibiotics would achieve higher antibiotic concentrations in the CSF and eliminate the bacteria more quickly.

Only one randomised or quasi-randomised trial related to this topic could be identified. The updated literature searches in June 2007 and May 2011 did not identify any additional studies for inclusion. The included study did not strictly fulfil all our selection criteria as the study included both neonates (69% of the infants were ≤ 29 days old) and older infants (31%). As the majority of infants enrolled were neonates we considered it appropriate to report on the results of this study. The randomised controlled study design included concealed allocation to the two interventions, thus avoiding a major threat to validity. It is unclear if the outcomes were assessed blinded to group. This is more of a concern regarding the long-term follow-up assessments among survivors than all-cause mortality, which is an undisputable outcome. The study authors do not provide enough information to draw any conclusion regarding long-term developmental outcomes (age at assessment; incidence and degree of motor, cognitive and sensory impairments). No imaging techniques were applied to ascertain any damage caused by the intraventricular taps.

There was no statistically significant reduction in the duration of culture positivity of CSF, the major underlying rationale for intraventricular antibiotics in infants with meningitis/ventriculitis.

With the markedly increased mortality in the group receiving intraventricular plus intravenous antibiotics compared to the group receiving intravenous antibiotics group alone, further trials in neonates are not justified. The increased mortality could be related to the procedure itself or to toxicity of the intraventricularly administered gentamicin (McCracken 1980). The increased mortality in the intraventricular antibiotics group is the likely reason why no further trials have been conducted.

AUTHORS' CONCLUSIONS

Implications for practice

In infants with meningitis and ventriculitis, intraventricular antibiotics in combination with intravenous antibiotics resulted in a three-fold increased RR for mortality compared to standard treatment with intravenous antibiotics alone and should be avoided. These conclusions are based on one trial that enrolled infants with gram-negative meningitis and ventriculitis.

Implications for research

Further trials comparing intraventricular plus intravenous antibiotics to intravenous antibiotics alone are not justified in this population.

ACKNOWLEDGEMENTS

![Cochrane Library logo] Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

REFERENCES

References to studies included in this review

McCracken 1980 *{published data only}*

* McCracken GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. *Lancet* 1980;**1**:787-91.

Mustafa MM, Mertsola J, Ramilo O, Saez-Llorens X, Risser RC, McCracken GH. Increased endotoxin and interleukin1-beta concentrations in cerebrospinal fluid of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. *The Journal of Infectious Diseases* 1989;**160**:891-5.

Additional references

Anderson 1990

Anderson SG, Gilbert GL. Neonatal gram negative meningitis: a 10-year review, with reference to outcome and relapse of infection. *Journal of Paediatrics and Child Health* 1990;**26**:212-16.

Arnell 2007

Arnell K, Enblad P, Wester T, Sjolin J. Treatment of cerebrospinal fluid shunt infections in children using systemic and intraventricular antibiotic therapy in combination with externalization of the ventricular catheter: efficacy in 34 consecutively treated infections. *Journal of Neurosurgery* 2007;**107**:213-9.

Baumgartner 1983

Baumgartner ET, Augustine RA, Steele RW. Bacterial meningitis in older neonates. *American Journal of Diseases of Children* 1983;**137**:1052-4.

Bell 1989

Bell AH, Brown D, Halliday HL, McClure G, McReid M. Meningitis in the newborn - a 14 year review. *Archives of Disease in Childhood* 1989;**64**:873-4.

Dawson 1999

Dawson KG, Emerson JC, Burns JL. Fifteen years of experience with bacterial meningitis. *Pediatric Infectious Disease Journal* 1999;**18**:816-22.

Flexner 1913

Flexner S. The results of serum treatment in thirteen hundred cases of epidemic meningitis. *Journal of Experimental Medicine* 1913;**17**:553-76.

Franco 1992

Franco SM, Cornelius VE, Andrews BF. Long-term outcome of neonatal meningitis. *American Journal of Diseases of Children* 1992;**146**:567-71.

Harvey 1999

Harvey D, Holt DE, Bedford H. Bacterial meningitis in the newborn: a prospective study of mortality and morbidity. *Seminars in Perinatology* 1999;**23**:218-25.

Heath 2003

Heath PT, Yusoff NK, Baker CJ. Neonatal meningitis. *Archives of Disease in Childhood Fetal Neonatal Edition* 2003;**88**:F173-8.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hristeva 1993

Hristeva L, Booy R, Bowler I, Wilkinson AR. Prospective surveillance of neonatal meningitis. *Archives of Disease in Childhood* 1993;**69**:14-8.

James 1980

James HE, Wlash JW, Wilson HD, Connor JD, Bean JR, Tibbs PA. Prospective randomized study of therapy in cerebrospinal fluid shunt infection. *Neurosurgery* 1980;**7**:459-63.

Klein 2000

Klein JO. Bacterial meningitis and sepsis. Remington JS, Klein JO (eds) Infectious diseases of the fetus and newborn infant. Philadelphia: WB Saunders, 2000:943-98.

Klinger 2000

Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. *Pediatrics* 2000;**106**:477-82.

Lee 1977

Lee EL, Robinson MJ, Thong ML, Puthuchveary SD, Ong TH, Ng KK. Intraventricular chemotherapy in neonatal meningitis. *Journal of Pediatrics* 1977;**91**:991-5.

McCracken 1972

McCracken GH. The rate of bacteriologic response to antimicrobial therapy in neonatal meningitis. *American Journal of Diseases of Children* 1972;**123**:547-53.

McCracken 1982

McCracken GH, Nelson JD, Grimm L. Pharmacokinetics and bacteriological efficacy of cefoperazone, ceftriaxone, and moxalactam in experimental Streptococcus pneumoniae and Haemophilus influenzae meningitis. *Antimicrobial Agents and Chemotherapy* 1982;**21**:262-7.

Polin 2001

Polin RA, Harris MC. Neonatal bacterial meningitis. *Seminars in Neonatology* 2001;**6**:157-72.

Pong 1999

Pong A, Bradley JS. Bacterial meningitis and the newborn infant. *Infectious Disease Clinics of North America* 1999;**13**:711-33.

Quagliarello 1997

Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *New England Journal of Medicine* 1997;**336**:708-16.

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Ronan 1995

Ronan A, Hogg GG, Klug GL. Cerebrospinal fluid shunt infections in children. *Pediatric Infectious Disease Journal* 1995;**14**:782-6.

Salmon 1967

Salmon JH. Puncture porencephaly. Pathogenesis and prevention. *American Journal of Diseases of Children* 1967;**114**:72-9.

Scheld 1984

Scheld WM, Mandell GL. Landmark perspective. Sulfonamides and meningitis. *JAMA* 1984;**251**:791-4.

Stamos 1993

Stamos JK, Kaufman BA, Yogev R. Ventriculoperitoneal shunt infections with gram-negative bacteria. *Neurosurgery* 1993;**33**:858-62.

Unhanand 1993

Unhanand M, Mustafa MM, McCracken GH, Nelson JD. Gram-negative enteric bacillary meningitis: a twenty-one-year experience. *Journal of Pediatrics* 1993;**122**:15-21.

Watanabe 1978

Watanabe I, Hodges GR, Dworzack DL, Kepes JJ, Duensing GF. Neurotoxicity of intrathecal gentamicin: a case report and experimental study. *Annals of Neurology* 1978;**4**:564-72.

Whitehead 2001

Whitehead WE, Kestle JR. The treatment of cerebrospinal fluid shunts. Results from a practice survey of the American Society of Pediatric Neurosurgeons. *Pediatric Neurosurgery* 2001;**35**:205-10.

Wright 1981

Wright PF, Kaiser AB, Bowman CM, McKee KT Jr, Trujillo H, McGee ZA. The pharmacokinetics and efficacy of an aminoglycoside administered into the cerebral ventricles in neonates: implications for further evaluation of this route of therapy in meningitis. *Journal of Infectious Diseases* 1981;**143**:141-7.

References to other published versions of this review

Shah 2004

Shah S, Ohlsson A, Shah V. Intraventricular antibiotics for bacterial meningitis in neonates. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004496.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

McCracken 1980

Methods	Multicentre (20 institutions in the US and Latin America) randomised controlled trial Recruitment dates March 1976 to December 1979 Blinding of randomisation - yes (sealed numbered envelopes) Blinding of intervention - no Blinding of outcome measure assessment - cannot determine Completeness of follow-up - yes
Participants	87 infants were considered for enrolment 16 infants were found to be unacceptable for the following reasons: (1) CSF cultures from 6 infants were sterile or yielded non-enteric organisms; (2) the pathogens from 4 patients were known to be resistant in vitro to ampicillin and gentamicin before enrolment; (3) 2 infants died before treatment was started; (4) 2 infants' physicians would not allow their patients to be enrolled; (5) in 1 infant ventriculitis could not be distinguished from intraventricular haemorrhage and (6) 1 infant with Down's syndrome was excluded because of the difficulty in evaluating neurological and mental status after therapy The remaining 71 infants comprised the study population 52 infants (73%) had meningitis and ventriculitis at the time of enrolment and 19 infants (27%) did not have ventriculitis 16 of the 52 infants with ventriculitis were ≥ to 30 days old (31%). Thus 69% of the infants were 29 days or younger (close to the conventional definition of a neonate, i.e. < 28 days of age)
Interventions	Intraventricular antibiotics (n = 28): gentamicin 2.5 mg/day intraventricularly for a minimum of 3 days No intraventricular antibiotics (n = 24): no intraventricular drug or placebo

McCracken 1980 *(Continued)*

All infants in both groups received systemic antibiotics: for those ≤ 7 days, ampicillin 50 mg/kg q12h IV and gentamicin 2.5 mg/kg q12h IM or IV, for those > 7 days, ampicillin 70 mg/kg q8h IV and gentamicin 2.5 mg/kg q8h IM or IV

Outcomes	Mortality Days positive CSF cultures Long-term follow-up
Notes	19 infants had meningitis without ventriculitis. 9 of these were assigned to lumbar intrathecal gentamicin plus systemic antibiotics, and 10 to systemic antibiotics only. These 2 groups were not included in this review because intraventricular antibiotics were not tested in these infants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Tables of random permutations of 16 numbers for each institution
Allocation concealment (selection bias)	Low risk	Yes (sealed numbered envelopes)
Blinding (performance bias and detection bias) All outcomes	High risk	The intervention could not be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completeness of follow-up - yes
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was not available to us
Other bias	Low risk	Appears free of other bias

CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; q8h: quaque 8 hora (every 8 hours); q12h: quaque 12 hora (every 12 hours).

DATA AND ANALYSES

Comparison 1.   Intraventricular antibiotics for meningitis in infants receiving intravenous antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality during hospital stay	1	52	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [1.09, 10.74]
2 Duration of culture positivity of CSF (days)	1	52	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-2.67, 0.27]

Analysis 1.1. Comparison 1 Intraventricular antibiotics for meningitis in infants receiving intravenous antibiotics, Outcome 1 All-cause mortality during hospital stay.

Study or subgroup	Intraven-tricular	No intra-ventricular	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
McCracken 1980	12/28	3/24		100%	3.43[1.09,10.74]
Total (95% CI)	**28**	**24**		**100%**	**3.43[1.09,10.74]**
Total events: 12 (Intraventricular), 3 (No intraventricular)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.12(P=0.03)					

Favours intravent 0.1 0.2 0.5 1 2 5 10 Favours No intravent
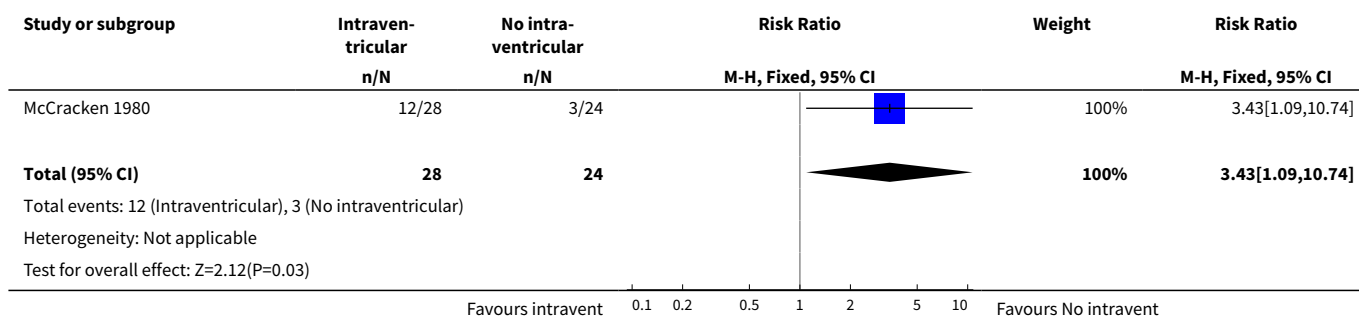
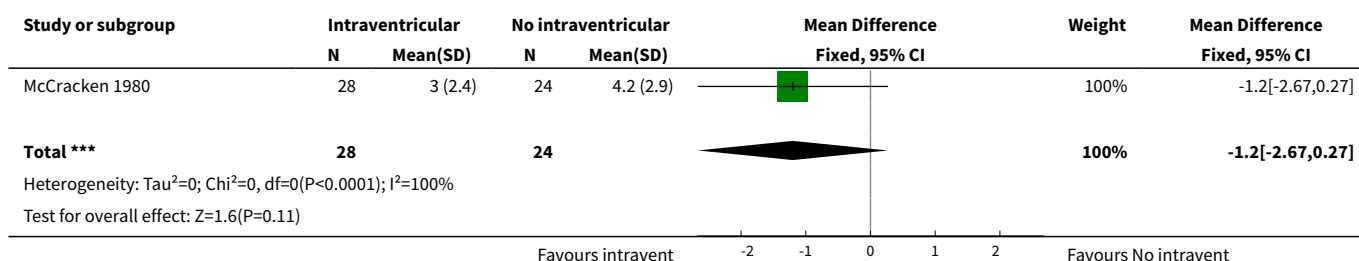### Analysis 1.2. Comparison 1 Intraventricular antibiotics for meningitis in infants receiving intravenous antibiotics, Outcome 2 Duration of culture positivity of CSF (days).

Study or subgroup	Intraventricular		No intraventricular		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
McCracken 1980	28	3 (2.4)	24	4.2 (2.9)		100%	-1.2[-2.67,0.27]
Total ***	**28**		**24**			**100%**	**-1.2[-2.67,0.27]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.6(P=0.11)							

Favours intravent -2 -1 0 1 2 Favours No intravent

APPENDICES

Appendix 1. Search Strategy - May 2011

PubMed

(meningitis AND intraventricular AND antibiotics) AND ((infant, newborn[MeSH] OR newborn OR neon* OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])) AND (("2006"[PDat] : "3000"[PDat]))

EMBASE

1 (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (607975)

2 (human not animal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (11910500)

3 (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1266847)

4 meningitis/ or meningitis.mp. (59009)

5 intraventricular antibiotics.mp. (28)

6 antibiotic agent/ (151738)

7 5 or 6 (151751)

8 1 and 2 and 3 and 4 and 7 (55)

9 limit 8 to yr="2007 -Current" (23)

CINAHL

(meningitis AND intraventricular antibiotics) and ((infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial))

Limiters - published date from: 1 January 2007 to present

the Cochrane Central Register of Controlled Trials

(infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW) and meningitis and "intraventricular antibiotics" from 2007 to 2011

Clinicaltrials.gov

Searched: (infant OR newborn) AND meningitis AND antibiotics

Controlled-trials.com

Searched: (infant OR newborn) AND meningitis AND antibiotics

W H A T ' S   N E W

Date	Event	Description
27 January 2020	Amended	Arne Ohlsson deceased.

H I S T O R Y

Protocol first published: Issue 4, 2003
Review first published: Issue 4, 2004

Date	Event	Description
9 June 2011	New citation required but conclusions have not changed	Updated search found no new trials. One retrospective study of interest for this review was identified and has been included (Arnell 2007). No changes to conclusions.
9 June 2011	New search has been performed	This review updates the existing review "Intraventricular antibiotics for bacterial meningitis in neonates" published in the Cochrane Database of Systematic Reviews.
10 June 2008	Amended	Converted to new review format.
4 July 2007	New search has been performed	This review updates the review "Intraventricular antibiotics for bacterial meningitis in neonates" published in The Cochrane Library, Issue 4, 2004 (Shah 2004). A repeat search of the literature was conducted on June 21, 2007. No new trials were identified.

Date	Event	Description
		The conclusions remain the same.
17 June 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All review authors contributed to all stages of the protocol and the full review. The update of the review was conducted by Arne Ohlsson (AO) and Vibhuti Shah (VS).

The May 2011 update was conducted centrally by the Cochrane Neonatal Review Group staff (Yolanda Montagne, Diane Haughton and Roger Soll).
Although no new trials were identified for this update in 2011, AO and SS identified one retrospective study of interest to this review (Arnell 2007) and included this information in the review. This update was reviewed and approved by Sachin Shah, Arne Ohlsson, and Vibhuti Shah.
>

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Department of Paediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

  Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Cerebral Ventriculitis [*drug therapy] [microbiology]; Gentamicins [*administration & dosage]; Gram-Negative Bacterial Infections [*drug therapy]; Injections, Intravenous; Injections, Intraventricular [adverse effects] [methods]; Meningitis, Bacterial [*drug therapy] [microbiology]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn